REMARKS

Claims 22, 23, 25 – 33 and 36 - 42 are currently pending and the subject of this Amendment. Claims 22, 27 and 31 have been amended. Claims 1 – 21 and 24 have been canceled. Claims 34 and 35 have been withdrawn from examination as being drawn to a non-elected invention. Support for the amendments can be found throughout the specification including the Drawings and Claims as filed originally. No new matter has been added.

Applicants respectfully reserve the right to pursue any non-elected, withdrawn, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

It is submitted that the claims, herewith and as originally presented were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

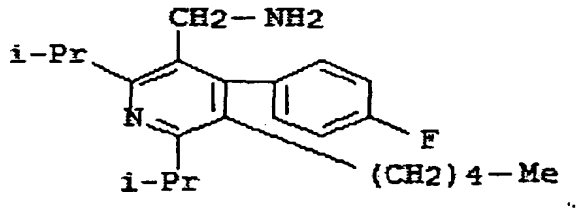
Applicant now turns to comments made by the Examiner in this Office Action as follows.

Office Action

1. Claims 6, 7, 12, 22, 23, 25, 27, 30, 31-33, 36-37, are rejected under 35 U.S.C. 103(a) as being unpatentable over Hcaplus 2001:278024 in view of Patani et. al .

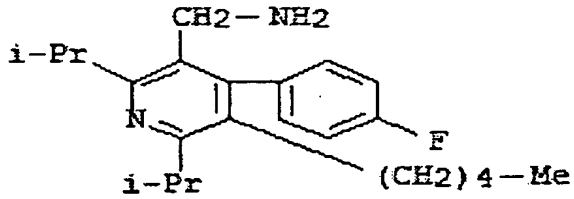
The Examiner states,

"Hcaplus 2001:278024 teaches the compound,



The difference between the prior art compound and the instantly claimed compounds is the teaching of an X moiety which is methyl rather than amino in the instant claim. Patani et. al. teaches that methyl and amino. At page 3152, Patani et. al. teaches that amino and methyl are bioisosteric replacements for hydrogen. Bioisosteres are able to elicit similar biological activity or enhanced pharmacological properties to the compounds that they are replacing due to similar chemical characteristics to these compounds. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare a bioisostere which like the instant compound, is a bioisosteric compound replacement for the compound when X is equal to

hydrogen. For instance, see the compound,



where a disclosed species is exemplified. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions.".

Applicants respectfully disagree. In the currently amended claims, Applicants have incorporated the subject matter of claim 24 into independent claim 22, thereby obviating the obviousness basis over Hcaplus in view of Patani et al. Applicants respectfully request reconsideration.

2. Claims 3, 6, 7, 12, 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

> The Examiner states, "Claims 3, 6, 7, 12, 27 recite the limitation "The compound of claim 1" in line 1. There is insufficient antecedent basis for this limitation in the claims."

Applicants have canceled claims 3, 6, 7 and 12, thereby obviating their basis of rejection. Claim 27 has been amended to claim its proper dependency, thereby obviating its basis for rejection. Applicants respectfully request reconsideration.

3. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I and Ia for treating obesity or impaired glucose tolerance is not enabled for preventing any of the diseases claimed, or treating diabetes, or diabetic complications. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized below.

> The Examiner states, "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).
>
> The main issues are the correlation between clinical efficacy for prevention and treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity and Applicants' *dipeptidyl peptidase IV inhibitory* assay.
>
> a) Determining if any particular claimed compound would treat or prevent any particular disease would require synthesis of the compound, formulation into a suitable dosage form, and testing these compounds in an assay known to be correlated to clinical efficacy of such treatment or prevention of the diseases claimed. This is a large quantity of experimentation given the large number of non-obvious compounds claimed. b) The direction concerning treating and preventing the diseases claimed diseases are found at pages 419 through 421. Dipeptidyl peptidase IV inhibitory assays are disclosed but it is unclear if this assay

is correlated to the prevention and treatment of the claimed diseases. c) There is no working example of treatment or prevention of the claimed diseases in any mammal or other animal. d) The nature of the invention is clinical treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity with the claimed compounds, which involves physiological activity. e) The state of the clinical arts in is that DPP-IV inhibitors have potential side effects with chronic use and will require ongoing scrutiny of the risk-benefit ratio for this therapy. See Abstract of Druker, page 2929. The large number of potential bioactive peptide substrates pose important questions regarding unanticipated side effects associated with the long-term use of DPP-IV inhibitors. See page 2935 of Drucker.

f) The artisan using Applicants invention would be a medicinal chemist with a PhD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the hundred of diseases embraced by the phrases "diabetic complications", "impaired glucose tolerance", "diabetes" or "obesity". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants have amended Claims 31 and 34 to delete the limitations relating to prophylaxis or treatment of diabetes and diabetic complications, leaving only impaired

glucose tolerance and obesity as disorders subject to methods of treatment with the specified pharmaceutical compounds. Applicants respectfully request reconsideration.

Lastly, Applicants respectfully request the rejoinder of Claims 34 and 35 on the basis that the subject matter of the claims are within the scope of a prior art search which is required for all other Claims under examination in this subject application.

CONCLUSION

In view of the claim amendments and remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested.

FEE AUTHORIZATION

The Commissioner is authorized to charge the extension fee and any other fees associated with this submission to our Deposit Account No. 04-1105, Reference 66540(46590). Any overpayment should be credited to said deposit account.

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Respectfully submitted,

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